



# Allergic Bronchopulmonary Aspergillosis: A Clinical Evaluation of 15 Patients and Successful Omalizumab Treatment of Five Patients

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## ABSTRACT

**Objective:** Allergic bronchopulmonary aspergillosis (ABPA) is an immunological lung disease caused by hypersensitivity reactions to *Aspergillus* antigen. Studies on the efficacy of omalizumab treatment in patients diagnosed with ABPA are limited to case reports and small series. Our aim was to evaluate the effectiveness of omalizumab treatment in ABPA in addition to clinical, radiological and serological characteristics these patients.

**Materials and Methods:** This study is a prospective observational one. It included clinical review of 15 patients diagnosed with ABPA and the successful omalizumab treatment of 5 of these patients. Patients receiving omalizumab therapy were assessed at baseline, after 1 year and 3 years of starting treatment.

**Results:** 15 patients (9 males, 6 females, mean age:  $48.26 \pm 9.92$  years) diagnosed as ABPA were enrolled. One patient had received antituberculosis medications prior to diagnosis. The mean serum total IgE level was  $1665 \pm 909$  IU/mL. The most common finding in thorax high-resolution computed tomography was central bronchiectasis. Omalizumab treatment was started in five patients with asthma and ABPA who have failed to respond to Global Initiative for Asthma step 4 treatment.

**Conclusion:** ABPA should be considered in patients with uncontrolled or severe asthma, despite appropriate asthmatic treatment. Recognizing ABPA is important, because early diagnosis can delay the development or prevent the bronchiectasis that causes fibrotic lung disease. Omalizumab is an effective therapy option in patients with asthma and ABPA who fail to respond to Global Initiative for Asthma step 4 treatment.

**Keywords:** Allergic bronchopulmonary aspergillosis, asthma, omalizumab

**ABBREVIATIONS:** **ABPA:** Allergic bronchopulmonary aspergillosis, **CF:** Cystic fibrosis, **Ig:** Immunoglobulin, **HRCT:** High-resolution computed tomography, **ACT:** Asthma control test, **SPT:** Skin prick test, **GINA:** Global Initiative for Asthma, **FEV1:** Forced expiratory volume in one second.

## INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disorder associated with hypersensitivity reaction against inhaled *Aspergillus fumigatus* antigen (1). The prevalence of this disease is still unclear and this is probably due to the lack of a uniform diagnostic criteria (2). ABPA frequently complicates

patients with asthma (1%-2%) and cystic fibrosis (CF) (5%-15%) (3). New or worsening cough or an increase in sputum production and wheezing may manifest when ABPA develops in patients with asthma or CF (4). ABPA can be misdiagnosed as pulmonary tuberculosis in asthmatic patients in the beginning because it is presented as wheezing, cough, sputum production, low-

grade fever, weight loss and malaise (5, 6). Skin testing with *Aspergillus fumigatus* antigen is important in the diagnosis of ABPA. However, the diagnosis should be supported by serology (7). Laboratory studies may show elevated serum levels of total immunoglobulin (Ig) E levels >1000 IU/mL, elevated *Aspergillus fumigatus* specific IgE or IgG levels and absolute eosinophil count >1000/mL (6). Central bronchiectasis is the most common high-resolution computed tomography (HRCT) scan finding although ABPA without bronchiectasis is also recognized (8). Patients who have clinical symptoms and positive

serologies suggestive of ABPA, but have no radiographic evidence of bronchiectasis, has been referred ABPA-serologic (3).

The diagnostic criteria for ABPA was first described by Rosenberg-Patterson in 1977 (9). It was later modified by Greenberger (4). Agarwal et al. proposed new diagnostic criteria in 2013 and later modified these in 2016 (10). Evolution of diagnostic criteria for ABPA is shown in Table I.

**Table I. Evolution of diagnostic criteria for allergic bronchopulmonary aspergillosis.**

Rosenberg-Patterson Criteria 1977 (9)	Greenberger Criteria 2002 (4)		Agarwal et al. 2013 (3)	Agarwal et al. 2016 (10)
Primary criteria (1-6 suggestive, +7 definite)	ABPA- Central bronchiectasis	ABPA-Seropositive	ABPA is diagnosed if all of the following criteria are met	ABPA is diagnosed if all of the following criteria are met
Primary	Essential criteria	Essential criteria		
1-Asthma	1-Asthma	1-Asthma	1-Predisposing condition asthma-or cystic fibrosis	1-Predisposing condition asthma-or cystic fibrosis, Chronic Obstructive Pulmonary Disease , post tuberculosis fibrotic cavitory disease
2-Peripheral eosinophilia				
3-Positive immediate skin reaction to <i>Aspergillus fumigatus</i>	2-Positive immediate skin reaction to <i>Aspergillus fumigatus</i>	2-Positive immediate skin reaction to <i>Aspergillus fumigatus</i>	2-Obligatory criteria: Positive type 1 <i>Aspergillus fumigatus</i> skin test or Elevated IgE against <i>Aspergillus fumigatus</i> (>0.35 kUA/L)	2-Obligatory criteria: Elevated IgE against <i>Aspergillus fumigatus</i> (>0.35 kUA/L) if this not available Positive type 1 <i>Aspergillus fumigatus</i> skin test
4-Positive precipitin test to <i>Aspergillus fumigatus</i>	3-Elevated specific IgE-/IgG to <i>Aspergillus fumigatus</i>	3-Elevated specific IgE-/IgG to <i>Aspergillus fumigatus</i>		
5-Increased total serum IgE	4-Serum IgE >417 IU/ml or 1000 ng/ml	4-Serum IgE >417 IU/ml or 1000 ng/ml	3-Obligatory criterion: Elevated total IgE levels >1000 IU/mL (or 2400 ng/ml)	3-Obligatory criteria: Elevated total IgE levels >1000 IU/mL (or 2400 ng/ml)
6-History of transient or fixed lung infiltrates	5-Central bronchiectasis			
7-Central bronchiectasis				
Secondary (supportive) criteria	Non-essential criteria		4-Other criteria: At least 2 of 3	4-Other criteria: At least 2 of 3
1- <i>Aspergillus fumigatus</i> in sputum (by culture or microscopy)	Chest X-ray infiltrates	Chest X-ray infiltrates	1-Radiographic pulmonary opacities (fixed/transient)	1-Radiographic pulmonary opacities (fixed/transient)
2-Brown plugs/flecks in sputum	Serum precipitating antibodies to <i>Aspergillus fumigatus</i>		2-Serum precipitating or IgG antibodies to <i>Aspergillus fumigatus</i>	2-Serum IgG>27mgA/L against <i>Aspergillus fumigatus</i>

The criteria described by Agarwal et al. had good sensitivity and specificity but Hamburger reported ABPA with normal serum IgE in a child with CF (11). Agarwal et al. used a latent class analysis to search the value of various diagnostic tests and criteria in identification of ABPA. They reported no diagnostic criteria had good sensitivity and specificity, and the diagnostic criteria described by Patterson et al. remain the gold standard for diagnosis of ABPA if six criteria are used (8). Finally, Agarwal et al. added new criteria such as *Aspergillus fumigatus* specific IgE level in which bigger accent has been laid on specific components in the diagnosis of ABPA (12).

Correct diagnosis should be made at an early stage to prevent chronic lung damage (3). Five stages of ABPA are as follows; acute, remission, exacerbation, corticosteroid dependent asthma, and fibrotic lung disease. Staging of the disease must be performed after establishing the diagnosis (14). The aim of the treatment of ABPA is to reduce acute inflammation and limit progressive lung injury. Systemic corticosteroids are the mainstay of treatment in the acute stage of ABPA, however chronic steroid use is related with the increased risk for side effects (13). Antifungal agents are used as an adjuvant or second line therapy in ABPA for both CF and asthma (3). Itraconazole has been shown to decrease attacks and eosinophilic airway inflammation. It is thought to be effective by decreasing the fungal load and reducing the antigenic stimulation and consequently the inflammatory response (15). Omalizumab has recently been reported that it might be an effective therapy option in patients with ABPA and asthma who fail to respond to Global Initiative for Asthma step 4 treatment while reports are limited to small series (16).

In this study, our aim was to evaluate the effectiveness of omalizumab treatment in ABPA in addition to clinical, radiological and serological characteristics these patients

## MATERIALS and METHODS

The present study is a prospective observational one. It included all ABPA patients diagnosed between 2014 and 2015 in the adult allergy clinic in Chest Diseases and Thoracic Surgery Training and Research Hospital. Pattersons criteria including asthma, positive immediate skin reaction to *aspergillus fumigatus*, increased serum total IgE level (IgE>417 IU/ mL), precipitating antibodies (IgG) in serum against *aspergillus fumigatus*, peripheral blood eosinophilia (eosinophil count >500 mm<sup>3</sup>), central bronchiectasis, transient or fixed lung infiltrates

additionally, increased *aspergillus fumigatus* specific IgE level (>0.35 kUA/L) were used to diagnose ABPA (9). All patients met at least six Pattersons diagnostic criteria recommended as the best diagnostic criteria if six criteria were used (12). Patients who did not give consent were excluded from in the study. Demographic features of patients were determined. A detailed clinical history consisting of other atopic diseases, history of past treatment, history of anti-tuberculosis medications in the past, family history of atopic diseases were obtained. Complaints of patients (cough, wheezing, shortness of breath and sputum production) were recorded.

Asthma control of patients was assessed with Asthma Control Test (ACT) questionnaire. According to the obtained ACT score, the patients' asthma status were described as uncontrolled (ACT score ≤19) or controlled asthma (ACT score >19) (17). The following investigations were performed: skin prick test for *Aspergillus fumigatus*, *Aspergillus fumigatus* specific IgE levels, total serum IgE levels, spirometry, chest radiograph, HRCT of the chest. Stool examination was performed in all patients to exclude parasitic infestations. Skin prick test (SPT) was performed using fungal antigens and patients with positive response were evaluated for ABPA. It was considered positive if there was a wheal response with a mean diameter of 3 mm or greater (18). SPT was performed using 3 common commercially prepared fungi including *Aspergillus fumigatus*, *Alternaria alternata*, *Penicillium antigen* (solution from Allergopharma, Germany). *Aspergillus* were measured by ImmunoCAP (Thermo Fisher Scientific Inc., Phadia AB, Uppsala, Sweden). For immunoCAP a positive result was defined as value ≥0.35 kU/L (19). Spirometry is performed to assess lung functions. Patients were classified as having mild (FEV1% predicted: 70-100), moderate (FEV1% predicted 50-60) and severe obstructive (FEV1% predicted < 50) lung disease After baseline measurement is obtained, the reversibility of the obstruction was assessed (20). Chest radiography and HRCT of the chest were the preferred radiological investigations.

Patients diagnosed with ABPA were treated with systemic corticosteroids and itraconazole, in addition to inhaled corticosteroids and bronchodilators. These patients were followed at 3 months intervals. We considered omalizumab treatment in severe persistent asthma and ABPA patients who have failed to respond to Global Initiative for Asthma step 4 treatment (21). Omalizumab was administered at dosages and dosing

frequency based on the patient's weight and initial total IgE levels as recommended for asthma (22). Patients were followed up at monthly intervals to assess the symptoms and adverse events due to medications. While the mean ACT score was obtained at baseline, after the first and third years; the mean forced expiratory volume in one second (FEV1) % was obtained at baseline and after the third year of omalizumab treatment.

The study was approved by the ethical committee of the Hospital (number: 1739) and informed consent was obtained from all participants.

### Statistical Analysis

Statistical analysis was performed by using SPSS ver. 17 (SPSS Inc., Chicago, IL, USA). Data are presented as mean  $\pm$  standard deviation (S.D.). Descriptive statistics were used to evaluate the demographic and clinical characteristics. One-sample t-tests were used for comparison of means. P values less than 0.05 were considered statistically significant.

### RESULTS

A total of 15 patients of ABPA were diagnosed in our allergy clinic in Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital. There were 9

males (60%) and 6 females (40%) with the mean age of  $48.26 \pm 9.92$  years (mean  $\pm$  SD) min-max, 32-70 years). The mean duration of asthma was  $15 \pm 9.08$  years (mean  $\pm$  SD) (min-max, 5-35 years). Only one (6.6%) patient had received anti-tuberculosis treatment before the diagnosis of ABPA. Nine patients (60%) had history of other allergic diseases and 6 (40%) had family history of allergic diseases.

The frequency of mild, moderate and severe obstruction in spirometry were 1 (6.6%), 4 (26.6%) and 10 (66%), respectively. There were fleeting or fixed radiological opacities in chest radiography and central bronchiectasis in HRCT 11 (73%) and 9 (60%) patients, respectively. Baseline mean percentage of the predicted FEV1 was  $42,51 \pm 12,9$  (mean  $\pm$  SD) (min-max, 20-62) and also the mean baseline ACT score was  $13,26 \pm 2,86$  (mean  $\pm$  SD) (min-max, 8-18).

The demographic features and baseline clinical characteristics of the patients in the study group are shown in Table II.

All patients had skin prick test positivity to *Aspergillus fumigatus*. The mean specific IgE levels for *Aspergillus fumigatus* was  $6.73 \pm 14,53$  kU/L ( $\pm$  SD). Serum total IgE levels were between 647 IU/mL and 3339 IU/mL and two patients had IgE levels below 1,000 IU/mL. The mean

**Table II. Demographic features and baseline clinical characteristics of the patients.**

Clinical characteristics	n(%)	
Age (years)*	$48.26 \pm 9.92$ years	(32-70)
Male sex	9 (60%)	
Duration of asthma (years)*	$15 \pm 9.08$	(5-35)
Past history of antituberculosis treatment	1 (6.6%)	
History of other allergic diseases	9 (60%)	
Family history of allergic diseases	6 (40%)	
Spirometry		
Normal	1 (6.6%)	
Mild obstruction	4 (26.6%)	
Moderate obstruction	10 (66%)	
Severe obstruction		
Fleeting or fixed radiological opacities in chest radiography	11 (73%)	
Bronchiectasis in HRCT	9 (60%)	
FEV1*	$42,51 \pm 12,94$	(20-62)
ACT score*	$13,26 \pm 2,86$	(8-18)

SD: Standard deviation, **min**: Minimum, **max**: Maximum, **HRCT**: High-resolution computed tomography, **FEV1**: Forced Expiratory Volume in 1 second, **ACT**: Asthma Control Test.

\* Mean  $\pm$  Standard deviation, minimum, maximum

absolute eosinophil count was  $692 / \text{mm}^3 \pm 346$  ( $\pm$  SD). Consequently all 15 patients met at least six Patterson criteria for the diagnosis of ABPA recommended as the best diagnostic criteria if six criteria were used (Table III).

Our study included patients who had asthma (10 severe persistent, 4 moderate persistent, 1 mild persistent). Respiratory symptoms included shortness of breath, cough and wheezing. Shortness of breath was the main symptom. Ten patients were treated with systemic corticosteroids and itraconazole in addition to inhaled corticosteroids and bronchodilators.

Five patients had stage IV (corticosteroid-dependent) ABPA because the patient's oral corticosteroids could not be tapered off completely and also, they failed to respond to Global Initiative for Asthma step 4 treatment.

Omalizumab treatment was started in 5 severe persistent asthma and ABPA patients. The mean duration of treatment with omalizumab was 36 months. Symptoms especially shortness of breath and wheezing improved dramatically in the third month of omalizumab treatment.

The mean ACT score was  $12.8 \pm 9.2$  at baseline and  $18.6 \pm 6.8$  in the first year and  $20.6 \pm 2.3$  in the third year and it has significantly increased after both 1 year and 3 years of starting omalizumab treatment compared with the baseline score ( $p < 0.001$ ).

The mean  $\text{FEV}_1$  % was  $41.16 \pm 14.77$  at baseline and  $54.11 \pm 17.18$  in the third year. It has statistically significantly increased in third year of starting omalizumab treatment compared to the baseline score ( $p < 0.001$ ) (Table IV).

**Table III. Patterson criteria for each patient (15 patients).**

Patient	Asthma	Immediate SPT positivity to <i>aspergillus fumigatus</i>	Serum IgE IU/ mL	Serum <i>aspergillus fumigatus</i> specific IgE kUA/L	Precipitating antibodies (IgG) against <i>Aspergillus fumigatus</i> , in serum	Eosinophil/ $\text{mm}^3$	Bronchiectasis	Transient or fixed lung infiltrates
1	Positive	Positive	3000	1.65	NP	550	Negative	Positive
2	Positive	Positive	818	2.10	NP	530	Negative	Positive
3	Positive	Positive	3000	53.70	NP	1005	Negative	Positive
4	Positive	Positive	1347	2.7	NP	430	Positive	Positive
5	Positive	Positive	2118	0.39	NP	590	Negative	Positive
6	Positive	Positive	647	1.39	NP	1280	Negative	Positive
7	Positive	Positive	1115	3.82	NP	80	Positive	Positive
8	Positive	Positive	2370	0.57	NP	230	Positive	Positive
9	Positive	Positive	1808	0.55	NP	530	Positive	Negative
10	Positive	Positive	832	0.74	NP	1020	Negative	Positive
11	Positive	Positive	1380	3.8	NP	1100	Positive	Negative
12	Positive	Positive	1417	0.07	NP	505	Positive	Positive
13	Positive	Positive	1153	0.89	NP	640	Positive	Positive
14	Positive	Positive	3339	26.52	NP	1119	Positive	Negative
15	Positive	Positive	1032	2.08	NP	775	Positive	Negative

NP: Not performed

**Table IV. Disease characteristics of the patients after the omalizumab treatment.**

Patient	ACT (baseline)	ACT (1 <sup>st</sup> year)	ACT (3 <sup>rd</sup> year)	FEV1 (baseline)	FEV1 (3 <sup>rd</sup> year)
1	14	18	20	34.39	53.85
2	12	18	21	42.3	55.6
3	8	15	19	39.41	50
4	14	22	23	62.7	72.1
5	16	20	20	27	39



Patients’ oral corticosteroid dosages, exacerbation and also the hospitalization rates were significantly decreased after omalizumab treatment. Omalizumab improved respiratory symptoms and provided discontinuation of systemic corticosteroids in all patients. Systemic corticosteroids were discontinued after 1 year in four patients, and after 3 years in one patient (Table V). Inhaled corticosteroids and bronchodilators doses were not significantly different in third year of starting omalizumab treatment.

**DISCUSSION**

ABPA is an immunological pulmonary disorder with various clinical, radiological and laboratory features (2). Published reports about ABPA are limited to case reports and small series in our country (21, 23). This is perhaps due to lack of uniform diagnostic criteria. ABPA is sometimes misdiagnosed as pulmonary tuberculosis. Interestingly in a study by Prasad et al. too many patients (91%) had been misdiagnosed as pulmonary tuberculosis and they had been treated with antituberculosis drugs before the diagnosis of ABPA (24). We had only one patient diagnosed with tuberculosis and receiving antituberculosis drugs. In 2013 Agarwal et al. suggested that the diagnostic criteria described by Patterson et al. remain the gold standard for the diagnosis of ABPA if six criteria are used (12). Thus, a total of 15 patients fulfilling at least six Patterson diagnostic criteria suggesting ABPA were included in our study. It has been suggested that ABPA mostly develops between third and fifth decades of life (25). Similarly the mean age of our patients was 48.26 ± 9.92 years. ABPA is predominantly seen in patients with asthma and also screening for ABPA should be performed in patients with uncontrolled or severe asthma, despite appropriate asthma therapy (22). Our study included patients who had asthma (10 severe persistent, 4 moderate persistent,

1 mild persistent). Five (33.3%) severe asthmatic patients frequently needed corticosteroids despite treatment with appropriate anti-asthmatic agents.

During the study period, patients were screened for ABPA using skin pick test with *Aspergillus fumigatus* and 15 patients had positive results. Serum specific IgE levels for *Aspergillus fumigatus* were elevated in all patients. Peripheral blood absolute eosinophil count was raised in 13 (86%) patients and it was >1000 cells/μl. While increased levels of total IgE are characteristic of ABPA different threshold levels have been used depending on the diagnostic criteria. A survey of the members of the American Academy of Allergy Asthma Immunology reported that there was a difference in the threshold levels of total serum IgE for the diagnosis of ABPA because 44.9% used ≥417 kU/L, whereas 42.0% used ≥1000 kU/L (26).

In our study serum total IgE ranged between 647 IU/mL - 3339 IU/mL and only two patients had IgE levels below 1,000 IU/mL. Central bronchiectasis was the predominant imaging finding in our study (60%) as in various studies (69-100% of the cases) (6, 27, 28). Consequently all of the 15 patients in our study met at least 6 criteria for the diagnosis of ABPA.

Treatment of ABPA includes use of corticosteroids for reducing inflammation and itraconazole to reduce aspergillus colonization. Patients who do not respond to corticosteroids antifungal medication can be used (29). Recently, reports have described effective results with the administration of omalizumab in patients with severe allergic asthma and ABPA (21, 29). In our study 5 (33.3%) patients with severe asthma had unsatisfactory response to anti-asthmatic agents. They frequently needed systemic corticosteroids for the control of their symptoms.

**Table V. Total monthly systemic corticosteroid use from baseline to the first and third years of omalizumab treatment.**

Patient	Average monthly systemic steroid (MP) dose at baseline	Average monthly systemic steroid (MP) dose at the first year of omalizumab treatment	Average monthly systemic steroid (MP) dose at the third year of omalizumab treatment
1	600 mg	Not needed	Not needed
2	720 mg	280 mg	Not needed
3	640 mg	Not needed	Not needed
4	680 mg	Not needed	Not needed
5	640 mg	Not needed	Not needed

MP: Methylprednisolone

We started omalizumab treatment in 5 severe persistent asthma and ABPA patients who have failed to respond to Global Initiative for Asthma step 4 treatment. Collins et al. observed a significant improvement in ACT symptom scores in patients with ABPA after omalizumab treatment (30). Aydın et al. reported that compared to the basal score, mean ACT score had increased after starting omalizumab treatment (21). Similar to these two reports, omalizumab treatment improved asthma symptoms and significantly increased the mean ACT score in both the first and third years in our study.

To date, many studies of patients with ABPA, treated with omalizumab had shown no significant changes in the mean FEV<sub>1</sub> % (31, 32). On the contrary a recent study from our country reported significant improvement in the mean FEV<sub>1</sub> % after omalizumab treatment in patients with ABPA (21). Similarly the mean FEV<sub>1</sub> % significantly increased in the third year of omalizumab treatment in our study.

In conclusion, treatment of severe asthmatic ABPA patients not responding to Global Initiative for Asthma step 4 with omalizumab created a steroid-sparing effect, improved asthma symptoms and pulmonary function parameters.

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